Ventilation/Perfusion SPECT Imaging-Diagnosing Other Cardiopulmonary Diseases Beyond Pulmonary Embolism

Bajc, Marika

2019-01

Bajc , M & Lindqvist , A 2019 , ' Ventilation/Perfusion SPECT Imaging-Diagnosing Other Cardiopulmonary Diseases Beyond Pulmonary Embolism ' , Seminars in Nuclear Medicine , vol. 49 , no. 1 , pp. 4-10 . https://doi.org/10.1053/j.semnuclmed.2018.10.012

http://hdl.handle.net/10138/309284
https://doi.org/10.1053/j.semnuclmed.2018.10.012

unspecified
publishedVersion

ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Ventilation/Perfusion SPECT Imaging—Diagnosing Other Cardiopulmonary Diseases Beyond Pulmonary Embolism

Marika Bajc, MD, PhD,* and Ari Lindqvist, MD, PhD†

Ventilation/perfusion single-photon emission computed tomography (V/P SPECT) is the scintigraphic technique recommended primarily for the diagnosis of acute pulmonary embolism (PE) and is golden standard for the diagnosis of chronic PE. Furthermore, interpreting ventilation and corresponding perfusion images enables pattern recognition of many other cardiopulmonary disorders that affect lung function and also allows quantification of their extent. Using Technegas for the ventilation imaging, grading of small airway disease in COPD is possible and the method is recommended for PE diagnosis in patients with severe COPD that is not possible with radiolabelled liquid aerosols. An optimal combination of nuclide activities, acquisition times for ventilation and perfusion, collimators, and imaging matrix yields an adequate V/P SPECT study in approximately 20 minutes of imaging time. The holistic interpretation strategy of V/P SPECT uses all relevant information about the patient and ventilation/perfusion patterns. PE is diagnosed when there is more than one subsegment showing a V/P mismatch representing an anatomic lung unit. Apart from PE, other pathologies should be identified and reported, such as obstructive lung disease, heart failure, and pneumonia according to the European Association of Nuclear Medicine guidelines.
Semin Nucl Med 49:4-10 © 2018 Published by Elsevier Inc.

Overview of Ventilation/Perfusion SPECT[1]

Ventilation/Perfusion SPECT (V/P SPECT) is the recommended method for the diagnosis of pulmonary embolism (PE) and it should be used whenever possible.[1] Apart from PE, other changes can be identified and reported, such as the signs of chronic obstructive pulmonary disease (COPD), pneumonia, left heart failure, chronic PE, pulmonary hypertension and suspicion of other parenchymal processes like tumors.[2-6] Recent studies have shown that for the ventilation study, Technegas particles have an advantage over radiolabeled liquid aerosols due to the better penetration to the periphery of the lung. Therefore, Technegas enables studies in patients with obstructive lung disease.[7] Radiolabeled macroaggregated human albumin is the imaging agent of choice for perfusion scintigraphy. An adequate V/P SPECT acquisition starting with ventilation and continuing with perfusion can be done in 20 minutes by using an optimal combination of radionuclide activities, collimators, and imaging matrix. It is recommended that the 1-day protocol starts with a ventilation examination, immediately followed by perfusion.[8] This allows for presentation of matching ventilation and perfusion slices in all projections. It also allows for rotating volume images based upon maximum intensity projections and quantification of V/P Quotient. V/P SPECT should be interpreted according to the European Association of Nuclear Medicine guidelines.

V/P SPECT Acquisition

Administration of the ventilation and perfusion agents should always be performed in the same position, preferably supine.

*Skåne University Hospital, Department of Clinical Sciences, University Hospital Lund, Lund, Sweden.
†Department of Pulmonary Medicine, Heart and Lung Center, Helsinki University Hospital and Helsinki University, Helsinki, Finland.
Address reprint requests to Marika Bajc, Department of Clinical Sciences, Skåne University Hospital, Lund, Sweden. E-mail: Marika.Bajc@med.lu.se

[1]Guest Editor's note: While most of the articles in this issue of *Seminars* uses the abbreviation "V/Q" when referring to ventilation and perfusion lung scanning, the term "V/P" is common in Sweden and some parts of Europe. "V/P" and V/Q" lung scans are the same. The term "V/P" has been retained here to reflect the authors' preference.

https://doi.org/10.1053/j.semnuclmed.2018.10.012
0001-2998/© 2018 Published by Elsevier Inc.

Table 1 Optimization of Ventilation and Perfusion Examinations in V/P SPECT

	Ventilation	Perfusion
Administration	Inhalation	IV injection
Radiopharmaceutical and administered activity	**[^{99m}Tc]-Technegas** 25-30 MBq to reach the lungs	**[^{99m}Tc]-MAA** 120-160 MBq
particle size	0.09 μm	15-100 μm
Time of Imaging	Approx 11 minutes	Approx 5 minutes
Acquisition protocol	General purpose collimator: 64 × 64 matrix, 60-64 steps for each head, 10 sec/step	General purpose collimator: 64 × 64 matrix, 60-64 steps for each head, 5 sec/step
Reconstruction	Iterative reconstruction—eight subsets and four iterations	Iterative reconstruction—eight subsets and four iterations

During inhalation, activity over the lungs should be monitored to ensure adequacy of pulmonary activity deposition. The procedure starts with ventilation scintigraphy. Large particles (>2 μm) are deposited mainly by impaction in large airways. Very fine particles, <1 μm, are mainly deposited in alveoli by diffusion. In comparison to radiolabeled liquid aerosols, Technegas shows significantly improved outcomes with deposition of radioaerosol in central airways and better penetration to the lung periphery, which is important for patients with obstructive airways disease. Thus, it enables a correct diagnosis of PE even in obstructive patients and its use is generally recommended.[3,7,9]

Perfusion tomography follows immediately after ventilation SPECT without changing the patient's position. After intravenous injection, the particles of size 15-100 μm are lodged in the pulmonary capillaries and in the precapillary arterioles in proportion to the perfusion.

To achieve adequate imaging quality with low radiation exposure in a short time, relationships between radioactivities, acquisition times, collimators, and matrices for SPECT imaging must be optimized. This problem has been systematically analyzed.[8] Doses of 25-30 MBq for ventilation studies and 120-160 MBq for perfusion studies were found to be optimal by using a general purpose collimator and 64 × 64 matrix. The total acquisition time is about 20 minutes. If a matrix of 128 × 128 is used, higher doses and/or longer acquisition times are required. This is not promoted as it does not yield images of significantly higher quality. To follow the good medical practice, radiation exposure should be minimized to the lowest level consistent with satisfactory image quality (Table 1).

When low-activity doses are used for V/P SPECT, as in the case of the pregnant or young female, it is essential to use an optimized iterative reconstruction. It is recommended to use ordered-subset expectation maximization with four iterations and eight subsets. Standard software can be used for the image presentation in coronal, sagittal, and transversal projections as well as for the presentation of rotating 3D images.[8]

We have developed a program to calculate and to display ventilation/perfusion quotient images to facilitate the image interpretation. For this purpose, ventilation is normalized to perfusion counts, and then the V/P quotient images are calculated.

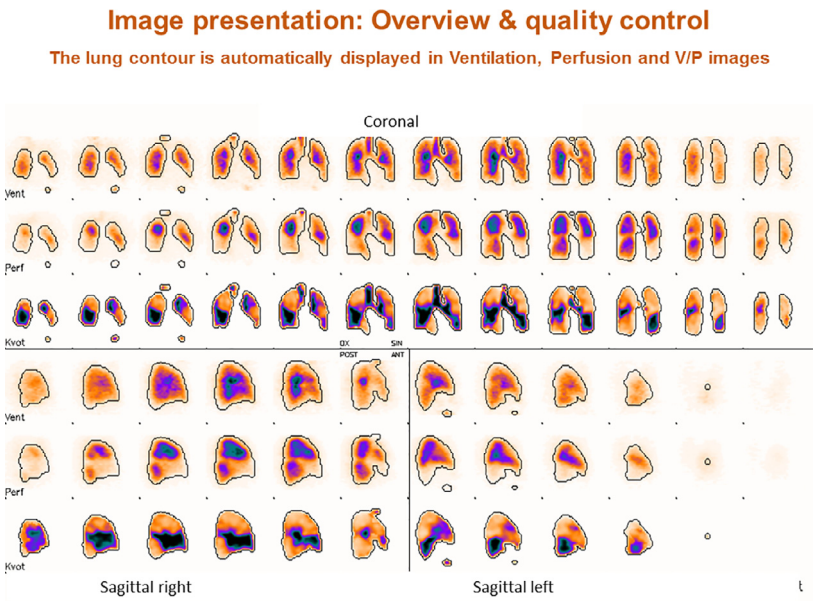

Figure 1 Overview of ventilation and perfusion SPECT images in coronal and sagittal slices. Ventilation and perfusion are carefully aligned to each other.

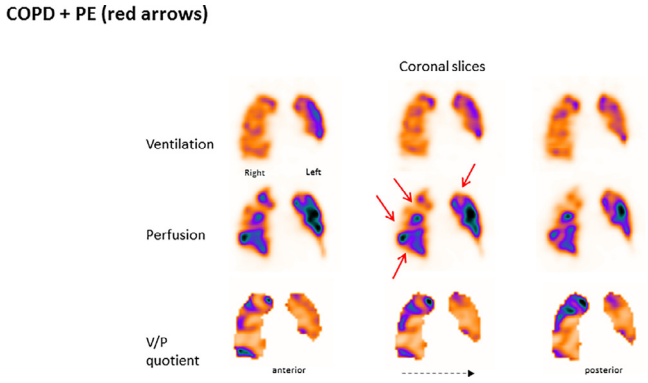

Figure 2 Patient with severe COPD and PE. Coronal slices: uneven distribution of ventilation with deposition of aerosols in small airways. Multiple perfusion defects are seen bilaterally (red arrows). COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism.

V/P quotient images facilitate also quantification of PE extent. Using this protocol, attenuation correction is not required.[8,10]

An overview of ventilation and perfusion in coronal and sagittal slices is useful for quality control and fast orientation regarding pulmonary pathology. It is important to present the matched images so that ventilation and perfusion are carefully aligned to each other (Fig. 1). This is greatly facilitated by the one session protocol with the patient in an unchanged position. The option to triangulate coronal, sagittal, and transverse slices is valuable for identification of matching and nonmatching ventilation and perfusion changes. Proper alignment is also a prerequisite for V/P quotient images. V/P quotient images facilitate recognition of mismatch and "reverse mismatch" patterns. This is important for the interpretation and quantification of the PE extent and for all ventilation and perfusion defects. However, quotient images are not a prerequisite for a high-quality V/P SPECT.

Holistic Interpretation

For V/P SPECT, interpretation criteria are as important as the imaging technique itself. In the holistic interpretation, all patterns of ventilation and perfusion as well as numbers of defects are described and interpreted and clinical probability is considered. The holistic interpretation gives a clear answer; yes or no regarding PE. Large V/P SPECT studies have shown conclusive reports in 96%-99% of cases.[11-15] This goal was not achieved with previous probabilistic criteria (PIOPED 1 and modified PIOPED).[16,17]

PE is diagnosed when there is more than one segment or two subsegments, showing a ventilation/perfusion mismatch representing an anatomic lung unit. Apart from PE, other pathologies should be identified and reported, such as broncho-obstructive disease, left heart failure, pneumonia, and suspicion of other parenchymal processes like tumors. Pitfalls exist both with respect to the imaging technique and scan interpretation.[1,18]

Chronic Obstructive Pulmonary Disease

COPD is frequently observed in patients suspected of PE, because COPD patients are at a higher risk of PE.[2,9,11] The

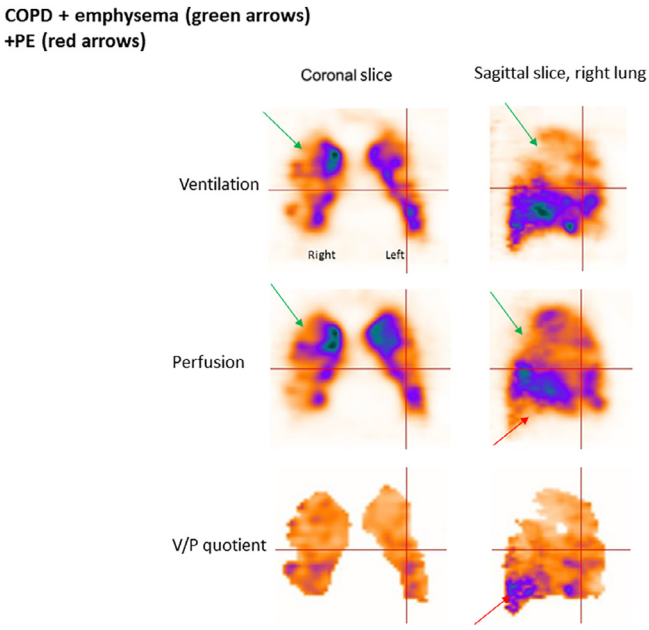

Figure 3 Patient with severe COPD, emphysema, and PE. Coronal and sagittal slices: uneven distribution of ventilation with central deposition of aerosols indicating severe degree of airway obstruction. In the right upper lobe is area with absent ventilation (better preserved perfusion), emphysema (green arrow). Corresponding perfusion images (middle row) show segmental perfusion defects (red arrows), PE, in the ventilated areas, well delineated on V/P quotient image. COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism.

rate of PE in patients hospitalized for acute exacerbation of COPD may be as high as 25%. PE accounts for up to 10% of deaths in stable COPD patients. Different to the PIOPED study, PE can be diagnosed even in the presence of COPD with V/P SPECT.

The characteristic of COPD is a general unevenness of ventilation. The degree of ventilation defect reflects varying severity of small airway disease and emphysema typical for COPD.[2,3,9,11,19,20] Emphysema is characterized by areas of absent/decreased ventilation with usually less pronounced perfusion defects (reverse mismatch).[3,21] Focal deposition of aerosol in central or peripheral airways may even locate sites of airway obstruction.[19] The degree of unevenness of aerosol distribution correlates with lung function tests.[3,22,23] The method gives the possibility to localize ventilation and perfusion impairment and also estimate total lung function.[24] It is noteworthy that there are no contraindications to V/P SPECT and that even very sick and breathless patients can be studied. Figure 2 shows coronal slices in a patient with a severe COPD and PE. Figure 3 shows coronal and sagittal slices in a patient with severe COPD, emphysema, and PE. The grading of obstruction in ventilation SPECT has been standardized (Fig. 4).

- Grade 1: Uneven radioaerosol distribution through the lung.
- Grade 2: Uneven radioaerosol distribution and reduced Technegas penetration to the periphery, with deposition of radioaerosols in small airways, seen as hot spots.

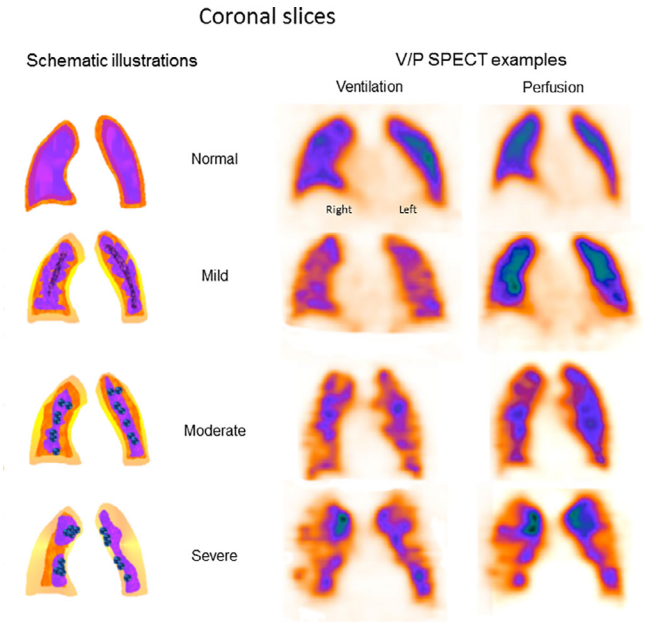

Figure 4 Degree of airway obstruction. Coronal slices: ventilation and corresponding perfusion images; normal pattern, mild, moderate, and severe COPD. COPD, chronic obstructive pulmonary disease.

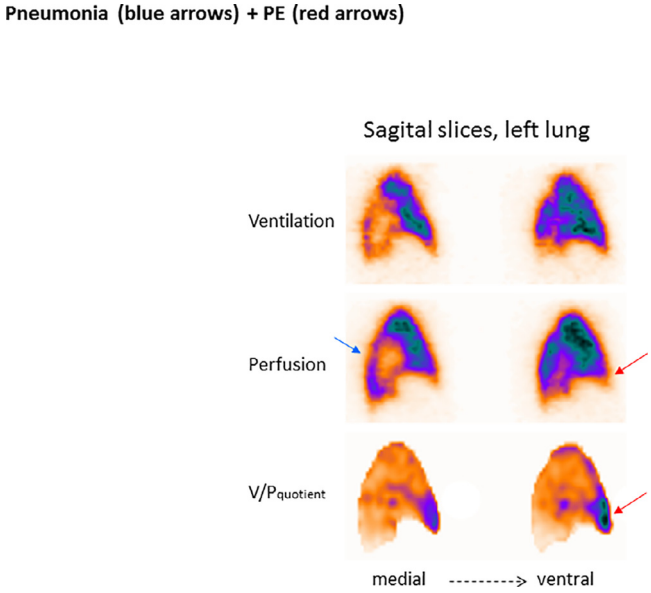

Figure 5 Patient with pneumonia and PE in the right lung. Sagittal slices: reduced/absent ventilation posteriorly with reduced perfusion in the same area. Preserved perfusion adjacent to the pleura, "stripe sign" (blue arrow). In the middle lobe, perfusion defect is seen (red arrow) in the ventilated area.

- Grade 3: Severely impaired Technegas penetration to the lung periphery and a central deposition of Technegas in large airways, usually with large areas of reduced/absent ventilation.

Moreover, V/P SPECT has a high sensitivity to showing an obstructive pattern in the lungs of many apparently healthy smokers[2].

Pneumonia

Pneumonia is also frequent finding in patients investigated for suspected PE. Figure 5 shows a patient with pneumonia and PE. Pneumonia is here a general term for conditions of lung inflammation often caused by a bacterial, viral, or fungal infection, where blood biomarkers are not sufficient in diagnosing pneumonia. Nonspecific clinical symptoms can lead to diagnostic problems.[25,26]

In pneumonia, V/P SPECT shows ventilation defects, which usually exceed perfusion defects known as reverse mismatch (reversed V/P mismatch).[27,28] Preserved perfusion along the pleural border peripheral to a central matched defect often termed a "stripe sign" is a specific characteristic of pneumonia (Fig. 5).[29] In a recent study that has followed patients with PE and pneumonia both clinically and with V/P SPECT, ventilation/perfusion changes typical for pneumonia and PE has normalized, confirming the diagnoses.[2] Dyspnoea was a common symptom in these patients. It can be caused by pneumonia as well as by PE or COPD. In some patients, V/P defects typical for pneumonia reduce the total lung function in the absence of any morphologic CT changes. Frequently, pneumonia is comorbid with PE. In these clinical scenarios, PE is frequently missed by CT.[2,30] This is important information because in general, current clinical and nuclear medicine practices do not recognize nor use V/P SPECT as a potential imaging method to diagnose or manage pneumonia.

Left Heart Failure

Antigravitational perfusion distribution from the posterior to anterior region indicates pulmonary congestion. The pattern was described already in 1966[31] and studied later.[2,4,32-34] As ventilation is usually less affected, the typical pattern is an antigravitational redistribution of perfusion and V/P mismatch in dorsal regions of the lung. This V/P mismatch has a nonsegmental pattern (does not conform to pulmonary vascular architecture) and should not be misinterpreted as PE. Figure 6 shows a patient with nonsegmental mismatch. The positive predictive value ≥88% for heart failure has been reported.[4] The power of V/P SPECT for diagnosis of heart failure was recently confirmed with regard to right heart catheterisation.[34]

Chronic PE

Chronic PE represents a condition in which pulmonary emboli do not resolve and the clinical presentation is often insidious. Chronic PE may be a progressive disease that develops in about 1%-5% of patients after an acute episode of PE, even in patients who have been treated.[35-38] It might be a consequence of repeated frequently

[2]Work in progress by the authors, presented at *Eur Respiratory Society* Annual Congress 2018

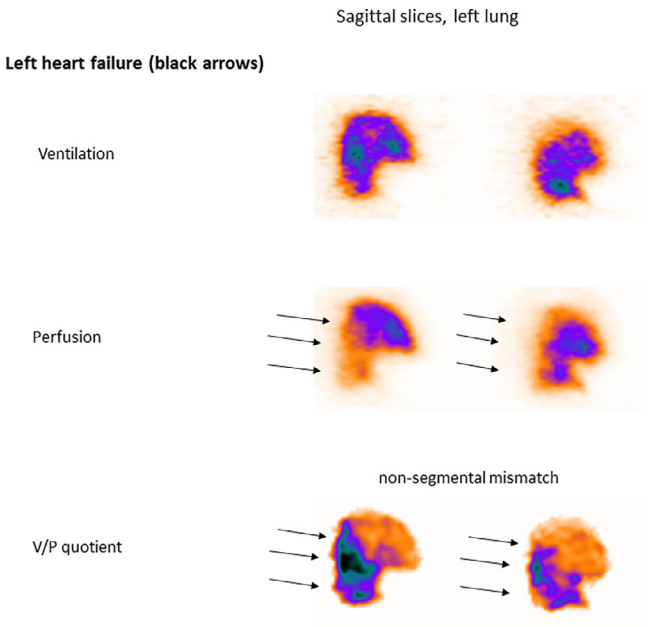

Figure 6 Patient with left heart failure. Sagittal slices: Antigravitational distribution of ventilation and more so of perfusion, causing nonsegmental V/P mismatch in the dorsal regions (black arrows).

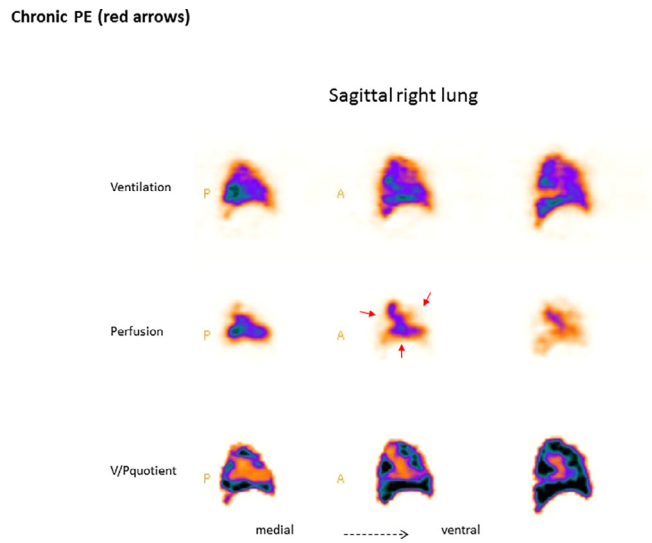

Figure 7 Patient with chronic pulmonary embolism. Sagittal slices: uneven ventilation. The corresponding perfusion images show hyperperfusion in the central part of the lung. Perfusion defects (red arrows) around the lung, clearly visible on V/P quotient images.

unrecognized small pulmonary emboli.[39] It may also lead to chronic thromboembolic pulmonary hypertension (CTEPH), right heart failure, and arrhythmia, which are frequent causes of death.

The value of V/P scintigraphy in this situation is well established but underutilized for this important diagnosis.[40–41] This has been confirmed in a head-to-head comparison between X-ray CT Pulmonary Angiography (CTPA) and planar scintigraphy with pulmonary angiography as a reference. Among patients with pulmonary hypertension, scintigraphy had a sensitivity of 96% and specificity of 90%, whereas CTPA had a sensitivity of 51%.[42] Soler et al confirmed that V/P SPECT had a higher sensitivity compared with CTPA.[43] For exclusion of CTEPH, V/P scintigraphy is the imaging test of choice.[38]

Pulmonary scintigraphy might also be able to differentiate among different types of CTEPH. A predominantly central subtype of CTEPH can be treated with a pulmonary endarterectomy. A predominantly peripheral subtype is not operable (Fig. 7). Sensitivity for detecting thromboembolic segments was significantly higher for V/P planar scintigraphy compared with CTPA: 96%-97.4% vs 51%, specificity 90%-95% vs 99%.[42] In central disease, the sensitivity of V/P SPECT was significantly higher than the sensitivity for V/P planar scintigraphy (63.5% ± 3.1% vs 42.7% ± 3.2%). The specificities of these two imaging modalities were not significantly different. In a similar setting, sensitivity of V/P SPECT was 62.0% ± 4.1% and that of CTPA 47.8% ± 2.9%.[43] Dual-energy CT perfusion and angiography, using a single acquisition, shows only moderate agreement (K = 0.44) with scintigraphy on the segmental level. Agreement between CTPA and scintigraphy ranged from fair (K = 0.31) to slight (K = 0.09).[44] In the treatment planning, even V/P SPECT under-represents the true extent of vascular obstruction from CTEPH.[43] Dual-energy CT is not able to supplement this information gap.

Conclusion

To take full advantage of the V/P SPECT potential, it is crucial to apply an optimal protocol for a single-session imaging of both ventilation and perfusion. This should be done by using low nuclide activities and by making a holistic interpretation.

Ventilation SPECT can be used to classify small airway disease in COPD. Together with perfusion SPECT, it can be used to evaluate the parenchymal damage (emphysema) in COPD. Ventilation and perfusion SPECT can be used to diagnose pneumonia and pulmonary congestion. To quantify pulmonary function, it is essential to measure ventilation and perfusion.

It is important to underline that using V/P SPECT, PE can be diagnosed in the presence of COPD and other pulmonary comorbidities. These advantages of V/P SPECT make it a suitable and desirable technique for diagnosing and following up PE. It is also an ideal technique to diagnose and follow up cardiopulmonary diseases like COPD, pneumonia, and left heart failure, which often cause similar kind of symptoms as PE.

References

1. Bajc M, Neilly JB, Miniati M, et al: EANM guidelines for ventilation/perfusion scintigraphy: Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Mol Imaging. 36:1356-1370, 2009

2. Begic A, Opankovic E, Cukic V, et al: Ancillary findings assessed by ventilation/perfusion tomography. Impact and clinical outcome in patients with suspected pulmonary embolism. Nuklearmedizin 54:223-230, 2015
3. Jogi J, Ekberg M, Jonson B, et al: Ventilation/perfusion SPECT in chronic obstructive pulmonary disease: An evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. Eur J Nucl Med Mol Imaging 93:1344-1352, 2011
4. Jogi J, Palmer J, Jonson B, et al: Heart failure diagnostics based on ventilation/perfusion single photon emission computed tomography pattern and quantitative perfusion gradients. Nucl Med Commun 29:666-673, 2008
5. Bajc M, Gruning T: Comment on "State-of-the-Art Imaging in Pulmonary Embolism: Ventilation/Perfusion Single-Photon Emission Computed Tomography versus Computed Tomography Angiography-Controversies, Results, and Recommendations from a Systematic Review". Semin Thromb Hemost 43:902-903, 2017
6. Bajc M, Jonson B: Ventilation/perfusion SPECT—an essential but underrated method for diagnosis of pulmonary embolism and other diseases. Eur J Nucl Med Mol Imaging 36:875-878, 2009
7. Jogi J, Jonson B, Ekberg M, Bajc M: Ventilation-Perfusion SPECT with 99mTc-DTPA Versus Technegas: A Head-to-Head Study in Obstructive and Nonobstructive Disease. J Nucl Med 51:735-741, 2010
8. Palmer J, Bitzen U, Jonson B, et al: Comprehensive ventilation/perfusion SPECT. J Nucl Med 42:1288-1294, 2001
9. Nasr A, Lindqvist A, Bajc M: Ventilation defect typical for COPD is frequent among patients suspected forpulmonary embolism but does not prevent the diagnosis of PE by V/P SPECT. EC Pulmonol Respir Med 4:85-91, 2017
10. Bajc M, Olsson C-G, Palmer J, et al: Quantitative ventilation/perfusion SPECT (QV/P_{SPECT}): A primary method for diagnosis of pulmonary embolism editor. In: M.Freeman L (ed): Nuclear Medicine Annual, Philadelphia: Lippincott Williams&Wilkins, 173-186, 2004
11. Bajc M, Olsson B, Palmer J, et al: Ventilation/perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. J Intern Med 264:379-387, 2008
12. Gruning T, Drake BE, Farrell SL, et al: Three-year clinical experience with VQ SPECT for diagnosing pulmonary embolism: Diagnostic performance. Clin Imaging 38:831-835, 2014
13. Le Roux PY, Robin P, Delluc A, et al: V/Q SPECT interpretation for pulmonary embolism diagnosis: Which criteria to use? J Nucl Med 54:1077-1081, 2013
14. Leblanc M, Leveillee F, Turcotte E: Prospective evaluation of the negative predictive value of V/Q SPECT using 99mTc-Technegas. Nucl Med Commun 28:667-672, 2007
15. Lemb M, Pohlabeln H: Pulmonary thromboembolism: A retrospective study on the examination of 991 patients by ventilation/perfusion SPECT using Technegas. Nuklearmedizin 40:179-186, 2001
16. The PIOPED Investigators Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 263:2753-2759, 1990
17. Gottschalk A, Juni JE, Sostman HD, et al: Ventilation-perfusion scintigraphy in the PIOPED study. Part I. Data collection and tabulation. J Nucl Med 34:1109-1118, 1993
18. Bajc M, Neilly JB, Miniati M, et al: EANM guidelines for ventilation/perfusion scintigraphy: Part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/P(SPECT) and MDCT. Eur J Nucl Med Mol Imaging. 36:1528-1538, 2009
19. Jobse BN, Rhem RG, McCurry CA, et al: Imaging lung function in mice using SPECT/CT and per-voxel analysis. PLoS One 7:e42187, 2012
20. Jobse BN, Rhem RG, Wang IQ, et al: Detection of lung dysfunction using ventilation and perfusion SPECT in a mouse model of chronic cigarette smoke exposure. J Nucl Med 54:616-623, 2013
21. Jogi J, Markstad H, Tufvesson E, et al: The added value of hybrid ventilation/perfusion SPECT/CT in patients with stable COPD or apparently healthy smokers. Cancer-suspected CT findings in the lungs are common when hybrid imaging is used. Int J Chron Obstruct Pulmon Dis. 10:25-30, 2015
22. Bajc M, Markstad H, Jarenback L, et al: Grading obstructive lung disease using tomographic pulmonary scintigraphy in patients with chronic obstructive pulmonary disease (COPD) and long-term smokers. Ann Nucl Med 29:91-99, 2015
23. Norberg P, Persson HL, Schmekel B, et al: Does quantitative lung SPECT detect lung abnormalities earlier than lung function tests? Results of a pilot study. EJNMMI Res 4:39, 2014
24. Bajc M, Chen Y, Wang J, et al: Identifying the heterogeneity of COPD by V/P SPECT: A new tool for improving the diagnosis of parenchymal defects and grading the severity of small airways disease. Int J Chron Obstruct Pulmon Dis 12:1579-1587, 2017
25. Scherer PM, Chen DL: Imaging Pulmonary Inflammation. J Nucl Med 57:1764-1770, 2016
26. Ewig S, Birkner N, Strauss R, et al: New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. Thorax 64:1062-1069, 2009
27. Carvalho P, Lavender JP: The incidence and etiology of the ventilation/perfusion reverse mismatch defect. Clin Nucl Med 14:571-576, 1989
28. Li DJ, Stewart I, Miles KA, et al: Scintigraphic appearances in patients with pulmonary infection and lung scintigrams of intermediate or low probability for pulmonary embolism. Clin Nucl Med 19:1091-1093, 1994
29. Sostman HD, Gottschalk A: The stripe sign: A new sign for diagnosis of nonembolic defects on pulmonary perfusion scintigraphy. Radiology 142:737-741, 1982
30. Bajc M: Value of ventilation/perfusion SPECT detecting extensive pulmonary embolism in a patient with pneumonia. Thromb Haemost 93:993-994, 2005
31. Friedman WF, Braunwald E: Alterations in regional pulmonary blood flow in mitral valve disease studied by radioisotope scanning. A simple nontraumatic technique for estimation of left atrial pressure. Circulation. 34:363-376, 1966
32. Freeman LM, Krynyckyi B, Zuckier LS: Enhanced lung scan diagnosis of pulmonary embolism with the use of ancillary scintigraphic findings and clinical correlation. Semin Nucl Med 31:143-157, 2001
33. Pistolesi M, Miniati M, Bonsignore M, et al: Factors affecting regional pulmonary blood flow in chronic ischemic heart disease. J Thorac Imaging 3:65-72, 1988
34. Jogi J, Al-Mashat M, Radegran G, Bajc M, Arheden H: Diagnosing and grading heart failure with tomographic perfusion lung scintigraphy: validation with right heart catheterization. ESC Heart Fail 5:902-910, 2018
35. Lang IM, Pesavento R, Bonderman D, Yuan JX: Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 41:462-468, 2013
36. Kayaalp I, Varol Y, Cimen P, Demirci Ucsular F, Katgi N, Unlu M, et al: The incidence of chronic thromboembolic pulmonary hypertension secondary to acute pulmonary thromboembolism. Tuberk Toraks 62:199-206, 2014
37. Hoeper MM, Madani MM, Nakanishi N, Meyer B, Cebotari S, Rubin LJ: Chronic thromboembolic pulmonary hypertension. Lancet Respir Med 2:573-582, 2014
38. Gopalan D, Delcroix M, Held M: Diagnosis of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 26:160108, 2017
39. Poli D, Miniati M: The incidence of recurrent venous thromboembolism and chronic thromboembolic pulmonary hypertension following a first episode of pulmonary embolism. Curr Opin Pulm Med 17:392-397, 2011
40. Stricker H: Chronic thromboembolic pulmonary hypertension–a diagnostic and therapeutic update. Vasa 45:195-199, 2016
41. Klok FA, Delcroix M, Bogaard HJ: Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism. J Thromb Haemost 16:1040-1051, 2018
42. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, et al: Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a

treatable cause of pulmonary hypertension. J Nucl Med 48:680-684, 2007

43. Soler X, Kerr KM, Marsh JJ, Renner JW, Hoh CK, Test VJ, et al: Pilot study comparing SPECT perfusion scintigraphy with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. Respirology 17:180-184, 2012

44. Dournes G, Verdier D, Montaudon M, Bullier E, Riviere A, Dromer C, et al: Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. Eur Radiol 24:42-51, 2014